

101 Rec'd PCT/PTO 19 JUN 1998

FORM PTO-1390 (Modified)
(REV 10-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

98,392

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/091958

INTERNATIONAL APPLICATION NO.
PCT/GB96/03195

INTERNATIONAL FILING DATE
20 December 1996

PRIORITY DATE CLAIMED
21 December 1995

TITLE OF INVENTION

OPHTHALMIC TREATMENT

APPLICANT(S) FOR DO/EO/US

PHARMACIA & UPJOHN AB

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☐ Other items or information:

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO. PCT/GB96/03195	ATTORNEY'S DOCKET NUMBER 98,392
--	--	---

20. The following fees are submitted:				CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :					
<input type="checkbox"/>	Search Report has been prepared by the EPO or JPO	\$930.00			
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482)	\$720.00			
<input type="checkbox"/>	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	\$790.00			
<input checked="" type="checkbox"/>	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO	\$1,070.00			
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	\$98.00			
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$1,070.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30				\$130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	20 - 20 =	0	x \$22.00	\$0.00	
Independent claims	2 - 3 =	0	x \$82.00	\$0.00	
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$1,200.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).				<input type="checkbox"/>	\$0.00
SUBTOTAL =				\$1,200.00	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30				\$0.00	
TOTAL NATIONAL FEE =				\$1,200.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).				<input type="checkbox"/>	\$0.00
TOTAL FEES ENCLOSED =				\$1,200.00	
				Amount to be: refunded	\$
				charged	\$

- ☒ A check in the amount of **\$1,200.00** to cover the above fees is enclosed.
- ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-2490** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Steven J. Sarussi
McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Suite 3200
Chicago, IL 60606

SIGNATURE

Steven J. Sarussi

NAME

32,784

REGISTRATION NUMBER

June 19, 1998

DATE

481106 PGPPTO 19 JUN 1998

09/091958

UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 98,392)

PATENT

In the Application of:)
)
Pharmacia & Upjohn AB) Group Art Unit:
) Unassigned
International Application No.)
PCT/GB96/03195) Examiner:
) Unassigned
Filed: December 20, 1996)
)
For: OHPHTHALMIC TREATMENT)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to the examination of the above-identified patent application, please amend the above-identified patent application as follows:

IN THE CLAIMS:

Please amend claims 3, 5, 7, 9, 11, 13 and 14 as follows:

3. (Amended) A dosage form according to Claim 1 [or Claim 2] wherein the jet or droplet is of a size sufficient to sustain its momentum in transmission from a delivery device to a target site.

5. (Amended) A dosage form according to [any preceding] Claim 1 wherein the jet or each droplet has a diameter in the range 100 to 800 μm .

662090-85676650

7. (Amended) A dosage form according to [any preceding] Claim 1 in which the total volume of treatment fluid does not exceed 10 μ l.

9. (Amended) A method of ophthalmic treatment comprising delivering to an eye a dosage form according to [any preceding] Claim 1.

11. (Amended) A method according to Claim 9 [or Claim 10] wherein the dosage is directed at a particular site in the eye.

13. (Amended) A method according to Claim 12 wherein the mean diameter of the jet and/or droplets is in the range 100 μ m to 800 μ m [, preferably 200 μ m to 400 μ m].

14. (Amended) A method according to claim 12 [or 13] wherein the total volume of treatment liquid in the dosage form does not exceed 10 μ l.

Please add new Claims 16-20.

16. A dosage form according to Claim 3 wherein the jet or each droplet has a diameter in the range 100 to 800 μ m.

17. A dosage form according to Claim 3 wherein the jet or each droplet has a diameter in the range 200 to 400 μm .

18. A dosage form according to Claim 17 in which the total volume of treatment fluid does not exceed 10 μl .

19. A method of ophthalmic treatment comprising delivering to an eye a dosage form according to Claim 8.

20. A method according to Claim 12 wherein the mean diameter of the jet and/or droplets is in the range of 200 μm to 400 μm .

REMARKS

The claims have been amended to remove multiple-dependencies. New claims 16-20 have been added. These new claims find express support in the original claims. Thus, no new matter is added by this amendment.

Applicants respectfully solicit allowance of the claims as amended and passage of the case to issue. Should the examiner believe that a discussion of this matter would be helpful, he is invited to telephone the undersigned at (312) 913-0001.

Respectfully submitted,

By: 

Steven J. Sarussi
Reg. No. 32,784
McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

Dated: June 19, 1998

09/091958

1

OPHTHALMIC TREATMENT

This invention relates to ophthalmic treatment and more particularly, to dosage forms useful in such treatment. The invention is concerned only with liquid treatment substances.

5 Ocular medication is most frequently administered as eye drop solutions. The typical volume of an eye drop has been found to range from 25 μ l to 50 μ l. Under normal conditions, in the open eye the human tear volume remains relatively constant at around 7 μ l, with
10 continuous drainage of tear fluid (via the nasolacrimal canal) being replaced by the tear glands. The tear volume can increase to about 30 μ l before overflowing occurs and the excess fluid is lost either through the nasolacrimal duct or by spillage onto the cheek.
15 Blinking reduces this maximal volume to say, 10 μ l. Thus the addition of large volumes of liquid such as those presented in commercial eyedrops will result in the rapid elimination of the active agents from the eye with typically 80-90 % of an instilled drop being lost
20 within one minute. Drug which drained through the highly vascular nasolacrimal duct can be absorbed into the systemic circulation as a bolus dose and therefore by-pass hepatic metabolism.

25 The recent use of β -blocking agents in ophthalmology has highlighted the disadvantages associated with this rapid drainage process, with serious life threatening side-effects such as bradycardia, bronchospasm and even heart failure being induced in susceptible patients. In addition, research
30 has also shown that the rate at which instilled solutions are drained from the eye varies directly with the instilled volume i.e. the larger the instilled volume, the more rapidly it is removed from the precorneal regions of the eye. These findings have led

to the suggestion that a higher concentration of drug in as small a volume as is practicable would be beneficial. In one study published in the American Journal of Ophthalmology 85, 1978 pp 225 to 229; Ocular bioavailability and systematic loss of topically applied ophthalmic drugs, by Thomas Patton and Michael Francoeur, it was reported that when using a 5 μ l eye drop loaded with 26.1 μ g of pilocarpine nitrate, the fraction of drug absorbed into the eye was 0.41 μ g, leaving 25.7 μ g available for potential systemic absorption. A similar calculation using a 25 μ l drop loaded with 67.8 μ g of pilocarpine nitrate, revealed that 0.36 μ g had penetrated the eye, thus leaving 67.4 μ g to be absorbed systemically. From this kind of study it can be concluded:

1. That an argument could be made for the use of smaller instilled volumes of eye drops than are normally delivered by most commercial ophthalmic droppers. Drainage loss would be minimised; contact time increased and hence the potential exists for improved drug activity.
2. Due to reduced drainage, less total volume of eye drop solution, and hence less drug need be used, therefore reducing the risk of systemic side-effects, whilst improving cost efficiency due to less wastage.

The research work referred to above is restricted to the use of ophthalmic solutions delivered as instillates. Surprisingly, we have found that the ocular bioavailability of ophthalmologically active compounds can be further enhanced by delivery to the eye in the form of a jet or stream of droplets.

Particularly, we have found that smaller quantities of the same treatment liquid, when delivered in this manner can have the same or an improved pharmacological effect.

Accordingly, the present invention provides a dosage form useful in ophthalmic treatment, comprising a jet or stream of droplets of treatment fluid, the jet or each droplet having an ophthalmologically active compound in suspension or solution, normally an aqueous solution. The jet or stream can be directed or targeted at a chosen site in an eye; eg, cornea, anterior bulbar conjunctiva, posterior bulbar conjunctiva or palpebral conjunctiva where the active compound can be most readily absorbed.

While dosage forms according to the invention can be delivered vertically, under the force of gravity, preferred forms are also suitable for horizontal delivery. In such forms, the jet or each droplet is of a size sufficient to sustain its momentum in transmission from a delivery device to a target site. Preferably, the size of the jet or each droplet is sufficient to sustain its momentum along a substantially horizontal path of 5 cm in length from a discharge velocity of up to 25 m/sec from a delivery device. A typical minimum discharge velocity is 5 m/s. As a general guide jet/droplet diameters in the range 20 to 1000 μm are suitable in the practice of the invention. A typical mean diameter for these purposes is in the range 100 to 800 μm , preferably 200 to 400 μm . This narrower range is a preferred guide, and in practice may not be critical. The efficacy of this invention is not adversely affected if the mean diameter is outside of this limit.

The enhanced bioavailability of ophthalmologically active compounds in dosage forms according to the invention enables the use of even smaller total volumes of treatment fluid than proposed in the eye drop study discussed above. Typically, the total volume of treatment fluid in a dosage form according to the invention does not exceed 20 μl , preferably no greater than 10 μl , and most preferably, in the range 3 to 8 μl .

The discharge of such a small volume from a delivery device at a suitable velocity to create the jet or stream will normally beat the "blink response" and result in a high percentage of the active compound in the treatment fluid performing its intended function. In other words, the entire volume can be delivered to the chosen site on the eye before the patient blinks to disperse the received fluid.

Treatment fluid used in dosage forms of the invention can additionally contain excipients to prolong the residence time in the cul-de-sac (the conjunctival sac), and thereby further enhance bioavailability. Suitable excipients include viscosity modulators, polymers, gelling agents and thickeners.

The invention will now be described with reference to the following examples.

Example 1 EPHEDRINE

Six white New Zealand rabbits were administered with the following dosage regimen:

I → 25 μ l of 1 % aqueous ephedrine hydrochloride solution (250 μ g) via pipette (instillate)

II → 5 μ l of 5 % aqueous ephedrine hydrochloride solution (250 μ g) via pipette (instillate)

III → 5 μ l of 5 % aqueous ephedrine hydrochloride solution (250 μ g) in a jet/stream of droplets of diameter in the range 200 to 400 μ m.

Pupil diameter measurements were determined from photographs acquired using a Pentax ME super 35 mm camera fitted with a SMC Pentax 50 mm lens and a 2x converter. An aperture setting of 12, and a shutter speed of 1/15 was employed with a film speed of ISO 400 (Kodak Gold 400). The camera was held stationary on a tripod and positioned approximately 30-40 cm from the rabbits eye. Prior to each dosing period the animals

were acclimatised to experimental conditions (constant light intensity, minimal distractions) for 20 min. The rabbits were placed in restraining boxes and settled before photographs and baseline pupil diameters were determined 5 min prior to dosing.

Pupillary diameters were determined from the developed colour prints (6 x 4) using an electronic micrometer (Digimatic Caliper, Mitutoyo Corp., Japan). Absolute pupil diameters were established by comparing the pupil diameter with a scale of known magnitude placed next to and in the same plane as the pupil prior to photography. The maximum response ratio (RR_{\max}) for pupil dilation was then calculated from the photographs using the following relationship:

$(RR_{\max}) = (\text{pupil diameter time } t - \text{average pupil diameter time } 0) / \text{average pupil diameter time } 0$. The graph of Figure 1 was then plotted of mean values of RR_{\max} against time. Curves I, II, and III represent the results from use of the respective dosage regimen referred to above.

Results

It can be seen from Figure 1 that the mydriatic response obtained from the 5 μ l ocular droplet dosage form was more pronounced and maintained over a longer duration compared to both instillates; in terms of RR_{\max} values the response can be ranked as follows : 5 μ l ocular droplet stream > 5 μ l instillate > 25 μ l instillate.

Instillates are normally administered directly into the conjunctival sac with reflex blinking distributing the majority of the solution over the cornea. Even with small volume instillates, a substantial proportion of the solution is still emptied directly into the nasolacrimal drainage system. In using dosage forms of the invention targeted directly at the cornea our results showed that the solution uniformly covered the cornea with minimal splash-back upon impact, with a

gradual pooling of liquid towards the conjunctival sac. Blinking in these instances distributed the solution over the corneal surface even further. This comparative study clearly shows that small volume ophthalmic solutions delivered in a droplet stream enhanced the bioavailability of ephedrine in comparison to the instillate presented from many commercial eyedroppers. A similar effect would be expected using other ophthalmic drugs.

Example 2 PILOCARPINE HCl

Ten white New Zealand rabbits were treated with the following dosage regimen in a randomised cross-over study:

30 μ l of 1 % aqueous pilocarpine hydrochloride solution (300 μ g) was instilled via pipette into the conjunctival sac 5 μ l of 1 % aqueous pilocarpine hydrochloride solution (50 μ g) was applied as a jet and/or stream of droplets (with a diameter in the range of 200 μ m to 400 μ m) to the surface of the cornea.

In order to determine pupil diameters, a metallic rule with a circular aperture of known diameter was orientated perpendicular to, and at an appropriate fixed distance from, a video camera fitted with a macro lens (Sony V8 Pro-CDD-V100E) throughout the study. During miotic measurements, the animals were positioned such that the left eye was parallel to the ruler and equidistant from the video camera. The video camera was actuated to project and amplify images of both the reference aperture and left eye onto the monitor screen. The diameters of both the reference aperture and pupil were then measured on the screen using a ruler placed on the projected image at an angle of approximately 135-305 degrees. The value of the pupil diameter was then calculated by multiplying the projected screen pupil

diameter by the ratio of the actual reference diameter (8 mm) to the projected screen reference diameter (18 mm) .

Pupil measurements were taken at approximately 60, 45, 30 and 15 minute intervals prior to administration of the treatments to provide a baseline value, and then at 15 minute intervals for the first hour after dosing. Thereafter, the pupil diameter was measured at 30 minute intervals for a minimum duration of 4 hours after dose administration.

For the purpose of statistical analysis of variants between treatments, the following parameters were determined: RR max = (pupil diameter at time t - pupil diameter at time 0) / pupil diameter at time 0; T max = the first time point at which the smallest pupillary diameter was observed; and AUC (0-4 hours) = the area under the pupillary diameter vs. time curve between 0 and 4 hours after treatment.

All significance tests were two-tailed and were performed at the 5 % significance level. The statistical software SAS V607 and the PROC GLM procedure were used in the analysis.

Results

Pupil diameter measurements were taken over the time course of the experiments. Some variation in the pupil diameter could be seen in the predose data, with a significant (P=0.0001) decrease in mean diameter being observed for both treatments as a function of time. The Shapiro-Wilk test for normality revealed that the errors associated with the pupil diameter readings were independently and normally distributed. Pupil diameter measurements were also taken following pilocarpine administration. A reduction in pupil diameter was evident for both dose forms after 15 minutes. However, this effect started to disappear approximately 60-90

minutes after treatment and, after 120 minutes, the measurements had fully recovered to their predose levels.

5	Pilocarpine	AUC (0-4hours)	T max	RR max	
	Treatment	mmMin.	Min.	%	
	1 % 30 μ l large	3871 \pm 340*	25.5 \pm 15.2	12.5* \pm 4.0*	
	eyedrop				
	(300 μ g)				
10	1 % 5 μ l jet and/or				
	stream of droplets	3827 \pm 312*	24.0 \pm 12.3	23.7* \pm 5.2*	
	(50 μ g)				

* standard deviations of the mean

The table compares the two treatments in terms of their effects on RR max, T max and AUC. There was no statistically significant difference in the calculated values of RR max, T max or AUC between either of the treatments. Thus, this work demonstrates that an ophthalmic dosage form comprised of a jet and/or stream of droplets can produce an equivalent pharmacodynamic effect to a standard eyedrop with only 1/6 of the drug.

25 Example 3 PROPRANOLOL HCl (Ocular distribution study)

40 μ l of 0.5 % aqueous tritiated propranolol hydrochloride solution (200 μ g) was administered via pipette into the conjunctival sac of twelve New Zealand white rabbit eyes. Separately, 5 μ l of 4 % aqueous tritiated propranolol hydrochloride solution (200 μ g) was applied as a jet or stream of droplets (with a diameter in the range of 200 μ m to 400 μ m) to the surface (cornea and/or conjunctiva) of twelve different New Zealand white rabbit eyes.

Following each treatment, four eyes were enucleated after

15 minutes, four after 30 minutes and the remaining four after 60 minutes. In each case, the animals were humanely killed prior to the ocular enucleation procedure via an overdose of sodium pentobarbitol injected into a marginal ear vein. Each eye was then irrigated by instilling 100 μ l of normal saline into the conjunctival sac using an automatic pipette and immediately blotting away excess saline with paper tissue to remove any radioactivity in the tear film. Following enucleation and removal of the adnexal tissue, the cornea was washed with a second 100 μ l of normal saline. The aqueous humor was then quickly removed by paracentesis with a 1 ml syringe and 26G needle. To this was then added an equal volume of trichloroacetic acid (TCA) solution (10 % w/v) to bring the final concentration to 5 % w/v TCA. Both eyes were then dissected from the posterior pole to allow removal of the vitreous humor and the lens, whilst the iris-ciliary body was transferred to a tared sample tube. The cornea was then removed using a 12 mm trephine, and the limbal cornea and conjunctiva (with underlying sclera) cut free into a strip approximately 5 mm wide using a scalpel and scissors. Each sample was then weighed in a tared sample tube and at least 5 volumes of TCA (6 % w/v) added. All tissue samples were subjected to sonication for 5 minutes, then centrifuged at 10 000 g.min. to yield a supernatant. Each supernatant was then extracted 3 times with 3 volumes of ether and, after evaporation of residual solvent, the aqueous residue was sampled and added to 5 ml of FluoronSafe XE "Scintron" scintillation fluid (BDH Chemicals, UK). Radioactivity was then determined by counting in a Packard 1600DR beta-scintillation counter. Data gathered as counts per minute was then converted into disintegrations per minute (dpm), using external standardisation, and expressed as dpm per g of tissue after adjusting for the total radioactivity in each dose. Due to the small number of samples per time point per treatment, statistical analysis was not considered

appropriate for this study.

Results

The results of this study are summarised for the different ocular tissues in tables 1 to 4 below, where the values shown represent dpm (disintegrations per minute) per mg of tissue.

Table 1: Cornea

Propranolol Treatment	15 mins	30 mins	60 mins
0.5 % 40 μ l large eyedrop (200 μ g)	5579	3467	2945
4.0 % 5 μ l jet and/or stream of droplets (200 μ g)	5241	3766	1861

Table 2: Conjunctiva/sclera

Propranolol Treatment	15 mins	30 mins	60 mins
0.5 % 40 μ l large eyedrop (200 μ g)	2569	2838	1380
4.0 % 5 μ l jet and/or stream of droplets (200 μ g)	5286	2259	1673

Table 3: Aqueous humor

Propranolol Treatment	15 mins	30 mins	60 mins
0.5 % 40 μ l large eyedrop (200 μ g)	1310	960	705
4.0 % 5 μ l jet and/or stream of droplets (200 μ g)	1845	1176	607

Table 4: Iris-ciliary body

Propranolol Treatment	15 mins	30 mins	60 mins
0.5 % 40 μ l large eyedrop (200 μ g)	942	1033	799
4.0 % 5 μ l jet and/or stream of droplets (200 μ g)	2256	1482	586

Significant radioactivity was detected in all ocular tissues at all time points for both treatments.

Following dose administration the drug will initially
5 be absorbed into either the cornea or conjunctiva. It would then be expected to partition into the aqueous humor and finally reach the iris-ciliary body, which is the site of action for an ophthalmic beta blocker. The concentration of drug in this tissue is therefore of
10 paramount importance in terms of clinical efficacy, i.e. intra-ocular pressure (IOP) reduction. Moreover, recent literature reports (ref: S.A. Sadiq and S.A. Vernon, British Journal of Ophthalmology. 1996 Vol. 80, pp. 532-535) with the most widely used ophthalmic beta blocker, timolol maleate, suggest that the rate at which drug
15 saturates the ocular beta-adrenoceptors in the iris-ciliary body is also of considerable importance in terms of clinical efficacy. The rationale here is that rapid heavy blockade of the receptor sites maximises inhibition of aqueous humor secretion and, therefore, IOP reduction.
20

This fact is of considerable importance when interpreting the results from the present study. Thus, the level of propranolol reaching the iris-ciliary body early (i.e. at the 15 minute time point) from the jet and/or
25 stream of droplets was more than double that obtained from the eyedrop. Such a rapid and substantial accumulation of the beta blocker at its target site would be expected to produce a marked benefit in terms of beta-adrenoceptor inhibition and, therefore, IOP reduction. The
30 comparatively higher level of radioactivity in the iris-ciliary body from the eyedrop after 60 minutes probably reflected re-absorption from the local vasculature.

The concentrations of propranolol in the other tissues are not directly relevant from a therapeutic
35 viewpoint, as the iris-ciliary body is the only site of aqueous humor formation in the eye. Therefore, although the concentrations of propranolol in some of these other

09091950.060709

tissues are higher at certain timepoints from the eyedrop compared to the other dosage form, this is unlikely to be of direct relevance to the levels of beta-adrenoceptor inhibition and, therefore, the suppression of aqueous humor formation.

Ophthalmic treatment liquids that may be used with the invention may be aqueous or non-aqueous liquids, optionally containing a therapeutic compound or compounds such as:

1) Anti-glaucoma/IOP (intra-ocular pressure) lowering compounds

a) β -adrenoceptor antagonists, e.g. carteolol, cetamolol, betaxolol, levobunolol, metipranolol, timolol, etc.

b) Miotics, e.g. pilocarpine, carbachol, physostigmine, etc.

c) Sympathomimetics, e.g. adrenaline, dipivefrine, etc.

d) Carbonic anhydrase inhibitors, e.g. acetazolamide, dorzolamide, etc.

e) Prostaglandins, e.g. PGF-2 alpha and derivatives thereof such as latanoprost.

2) Anti-microbial compounds (including anti-bacterials and anti-fungals), e.g. chloramphenicol, chlortetracycline, ciprofloxacin, framycetin, fusidic acid, gentamicin, neomycin, norfloxacin, ofloxacin, polymyxin, propamidine, tetracycline, tobramycin, quinolines, etc.

3) Anti-viral compounds, e.g. acyclovir, cidofovir, idoxuridine, interferons, etc.

4) Aldose reductase inhibitors, e.g. tolrestat, etc.

5) Anti-inflammatory and/or anti-allergy compounds, e.g.

steroidal compounds such as betamethasone, clobetasone, dexamethasone, fluorometholone, hydrocortisone, prednisolone etc. and non-steroidal compounds such as antazoline, bromfenac, diclofenac, indomethacin, lodoxamide, saprofen, sodium cromoglycate, etc.

6) Artificial tear/dry eye therapies, comfort drops, irrigation fluids, etc., e.g. physiological saline, water, or oils; all optionally containing polymeric compounds such as acetylcysteine, hydroxyethylcellulose, hydroxymellose, hyaluronic acid, polyvinyl alcohol, polyacrylic acid derivatives, etc.

7) Diagnostics, e.g. fluorescein, rose bengal, etc.

8) Local anaesthetics, e.g. amethocaine, lignocaine, oxbuprocaine, proxymetacaine, etc.

9) Compounds which assist healing of corneal surface defects, e.g. cyclosporine, diclofenac, urogastone and growth factors such as epidermal growth factor, etc.

10) Mydriatics and cycloplegics e.g. atropine, cyclopentolate, homatropine, hysocine, tropicamide, etc.

11) Compounds for the treatment of pterygium, such as mitomycin C, collagenase inhibitors (e.g. batimastat) etc.

12) Compounds for the treatment of macular degeneration and/or diabetic retinopathy and/or cataract prevention.

13) Compounds for systemic effects following absorption into the bloodstream after ocular administration, e.g. insulin.

The above compounds may be in the form of free acids or bases or alternately as salts of these. Combinations

of compounds e.g. an anti-bacterial combined with an anti-inflammatory may be desirable for the optimization of therapy in some instances. The compounds may be formulated as aqueous or non-aqueous (e.g. oil) solutions or suspensions. Formulations may optionally contain other formulation excipients, for example, thickening agents such as gels, mucoadhesives and polymers, stabilisers, anti-oxidants, preservatives, pH/tonicity adjusters etc.

Devices suitable for delivering dosage forms in accordance with the present invention are described in our International Patent Application Nos. GB95/01482 and GB95/02040, now publication Nos. WO96/00050 and WO96/06581, to which reference is directed.

6640990-856T6060

CLAIMS

1. A dosage form useful in ophthalmic treatment comprising a jet or stream of droplets of treatment fluid, each droplet having an ophthalmologically active compound in suspension or solution.

2. A dosage form according to Claim 1 wherein the jet or each droplet has the active compound in aqueous suspension or solution.

3. A dosage form according to Claim 1 or Claim 2 wherein the jet or each droplet is of a size sufficient to sustain its momentum in transmission from a delivery device to a target site.

4. A dosage form according to Claim 3 wherein the jet or each droplet is of a size sufficient to sustain momentum along a substantially horizontal path 5 cms in length from a discharge velocity of up to 25 m/sec from the delivery device.

5. A dosage form according to any preceding Claim wherein the jet or each droplet has a diameter in the range 100 to 800 μm .

6. A dosage form according to Claim 5 wherein the jet or each droplet has a diameter in the range 200 to 400 μm .

7. A dosage form according to any preceding Claim in which the total volume of treatment fluid does not exceed 10 μl .

8. A dosage form according to Claim 7 in which the total volume of treatment fluid is in the range 3 to 8 μl .

9. A method of ophthalmic treatment comprising delivering to an eye a dosage form according to any preceding Claim.

10. A method according to Claim 9 wherein the eye is a human eye.

11. A method according to Claim 9 or Claim 10 wherein the dosage form is directed at a particular site in the eye.

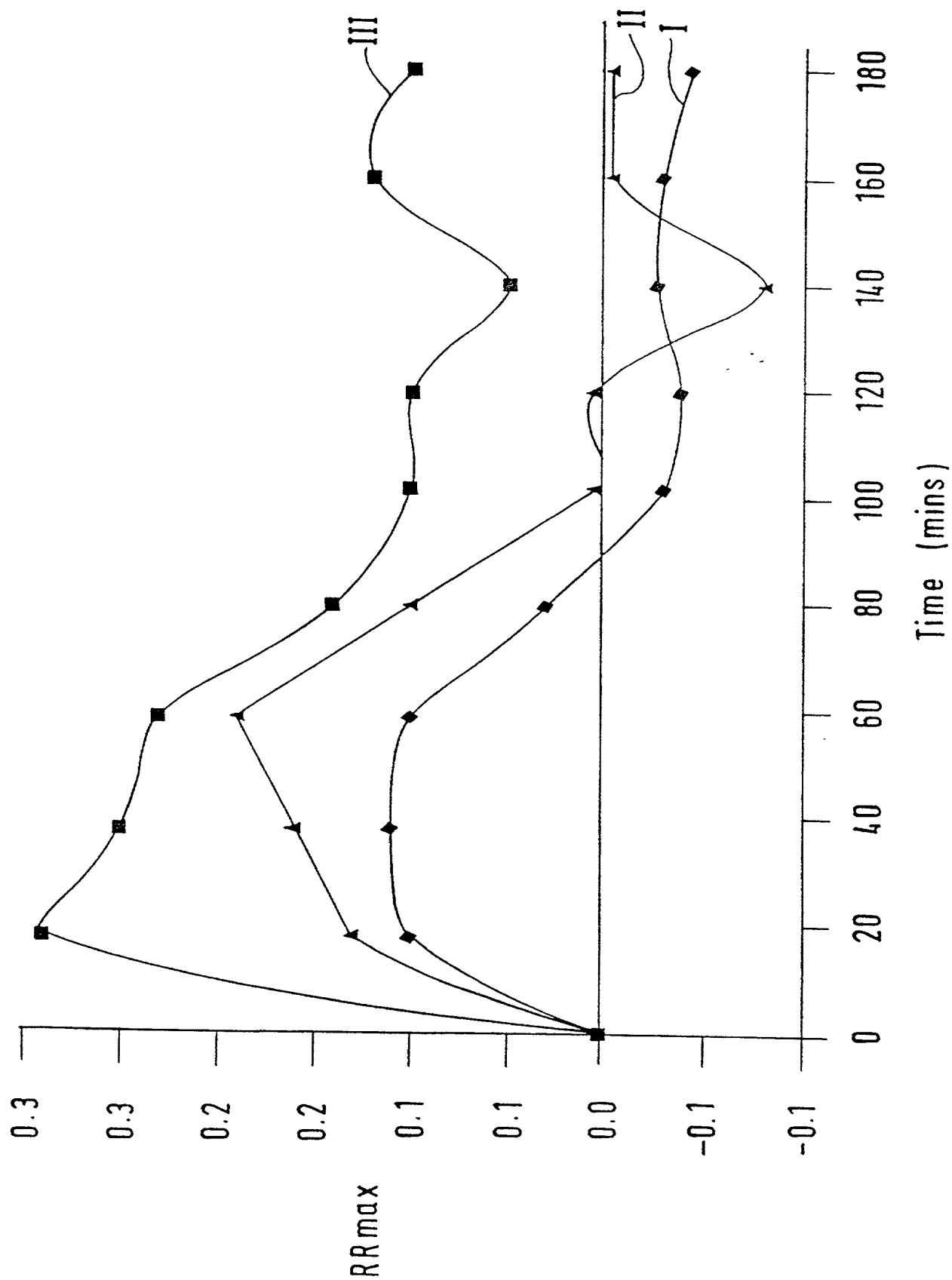
12. A method of increasing the ocular

13. A method according to Claim 12 wherein the mean diameter of the jet and/or droplets is in the range 100 μm to 800 μm , preferably 200 μm to 400 μm .

15. A method according to Claim 14 wherein the total volume of treatment liquid in the dosage form is in the range 3 μ l to 8 μ l.

1/1

662090" 856T6060



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

OPHTHALMIC TREATMENT

the specification of which is attached hereto unless the following space is checked:

☒ was filed on June 19, 1998, as United States Application Serial Number 09/091,958.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s):

	<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>
1.	9526150.9	Great Britain	December 21, 1995

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

	<u>Application Number</u>	<u>Filing Date</u>	<u>Status: patented, pending, abandoned</u>
1.	PCT/GB96/03195	December 20, 1996	Pending

I hereby appoint the following attorneys and agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

(B)
Denis A. Berntsen
John J. McDonnell
Daniel A. Boehnen
Bradley J. Hulbert
Paul H. Berghoff
Grantland G. Drutchas
Steven J. Sarussi
David M. Frischkorn
James C. Gumina
A. Blair Hughes
Thomas A. Fairhall
Emily Miao
Kevin E. Noonan
Leif R. Sigmund, Jr.
Lawrence H. Aaronson
Matthew J. Sampson

Reg. No. 26707
Reg. No. 26949
Reg. No. 28399
Reg. No. 30130
Reg. No. 30243
Reg. No. 32565
Reg. No. 32784
Reg. No. 32833
Reg. No. 32898
Reg. No. 32901
Reg. No. 34591
Reg. No. 35285
Reg. No. 35303
Reg. No. 35680
Reg. No. 35818
Reg. No. 35999

Curt J. Whitenack
Christopher M. Cavan
Michael S. Greenfield
Mark Chao
Roger P. Zimmerman
Anthoula Pomrening (agent)
George I. Lee
Patrick G. Gattari
Audrey L. Bartnicki
Amir N. Penn
Patrick J. Halloran (agent)
Joshua R. Rich
Thomas E. Wettermann
Robert J. Irvine
David S. Harper (agent)
G. Kenneth Smith

Reg. No. 36054
Reg. No. 36475
Reg. No. 37142
Reg. No. 37293
Reg. No. 38670
Reg. No. 38805
Reg. No. 39269
Reg. No. 39682
Reg. No. 40499
Reg. No. 40767
Reg. No. 41053
Reg. No. 41269
Reg. No. 41523
Reg. No. P41865
Reg. No. P42636
Reg. No. P43135

Address all telephone calls to Steven J. Sarussi at (312) 913-0001.

Address all correspondence to MCDONNELL BOEHNEN HULBERT & BERGHOFF, 300 South Wacker Drive, Chicago, Illinois 60606 USA.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: Jonathan Embleton

Inventor's signature: _____

Date: 15-4-99

Residence: 4 Beaufort Court, Chesterton Lane, Cirencester GL7 1WJ, GB

Citizenship: GB

Post Office Address: 4 Beaufort Court, Chesterton Lane, Cirencester GL7 1WJ, GB

Full name of second joint inventor: Richard Malcolmson

Inventor's signature: _____

Date: 17-4-99

Residence: 9 Ashburnham Close, Freshbrook, Swindon SN5 8RA GB

Citizenship: GB

Post Office Address: 9 Ashburnham Close, Freshbrook, Swindon SN5 8RA GB

52A BALSARAY DRIVE, BROOMHILL, GLASGOW G11 7DA

52A BALSARAY DRIVE, BROOMHILL, GLASGOW G11 7DA

3-00
Full name of second joint inventor: **Luigi Martini**

Inventor's signature: Luigi Martini

Date: 29 April 1999

Residence: ~~7 Dunsters Mead, Welwyn Garden City, Herts AL7 3JW, GB~~ **

Citizenship: GB

Post Office Address: ~~7 Dunsters Mead, Welwyn Garden City, Herts AL7 3JW, GB~~

** 9 Ranulf close, Old Harlow, CM17 0FX ^(w) 29 April 1999
GBX